Hepatitis C

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Investigations

- Viral Load
- Viral genotype
- HIV
- ALT
  - Normal v abnormal
- Liver Biopsy
  - Fibrotest/Fibroscan/

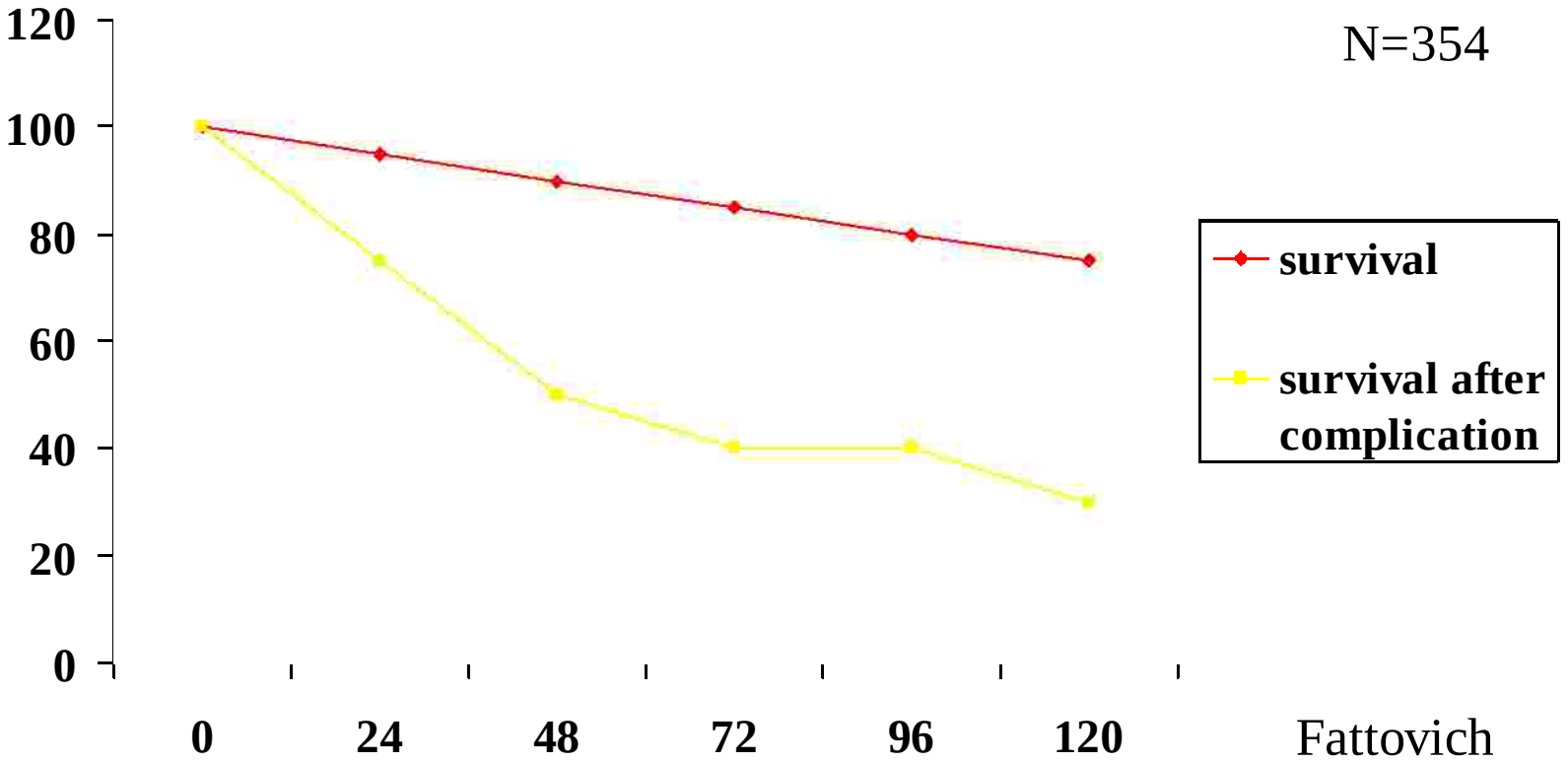
Natural History
Better than we initially thought

Study	Group	Exposure Interval (y)	Cirrhosis %		HCC %	Liver Death %
Vogt[9]	Children	17	mean, 2.1%	0.3	0	0
Kenny-Walsh[7]	Young women	17		2.0	0	0
Wiese[8]	Young women	20		0.4	0	0
Seeff[23]	Young men	45-50		5.9	0	0
Thomas[24]	IDU	9-15		1.0	0	2.1
Rodger[10]	Comm acq	25		4.0	0	1.0
Seeff[25]	PTH	23		15.0	1.9	2.8

Initial data *20% cirrhotic within 20yrs of infection*

Now *2-5% cirrhotic within 20yrs*

Probability of Survival following diagnosis of HCV cirrhosis



Fattovich Gastro 1997; 112: 463

Peginterferon alfa-2a + Ribavirin

	PEG-IFN	Standard IFN +Ribavirin	PEGIFN + Ribavirin	
All	29%	45%	56%	
Genotype 1	21%	36%	46%	**12 months**
Genotype 2/3	45%	61%	76%	**6 months**
Cirrhosis	21%	33%	43%	

Except if

- Ribavirin
  - Absolute
    - Pregnancy
    - End stage renal disease
    - Hb <11g/dl
  - Relative
    - Unstable coronary artery disease
- Interferon
  - Absolute
    - Alcohol misuse
    - Untreated depression
    - Decompensated cirrhosis
    - Severe neutropaenia or thrombocytopaenia
  - Relative
    - Neutrophil < 1000/dl
    - Platelets < 75 x109/l

Side-effects

- Road rage
- Suicide (often no warning signs)
- Pushed back into drugs
- Skin rashes
- Thyroid disease
- Not able to work
  - Airline pilots
  - Fatigue/depression/iritability
- Diarrhoea
- Decompensated cirrhosis

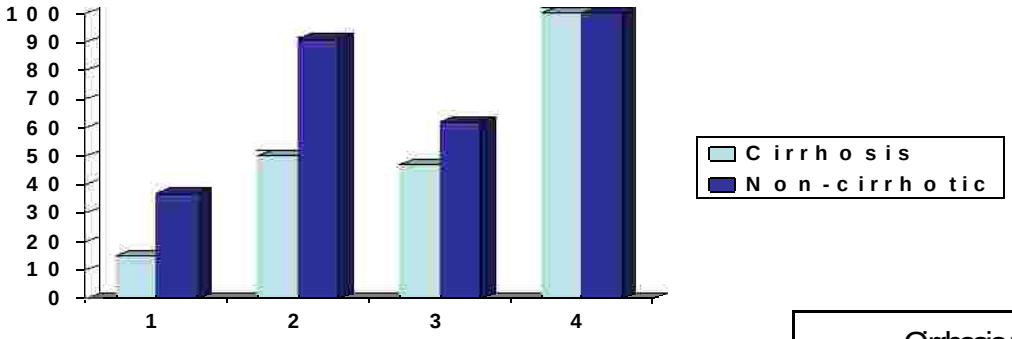
Worth retreating
In some cases

Comparison
Audits 2001-6 with 2006-7

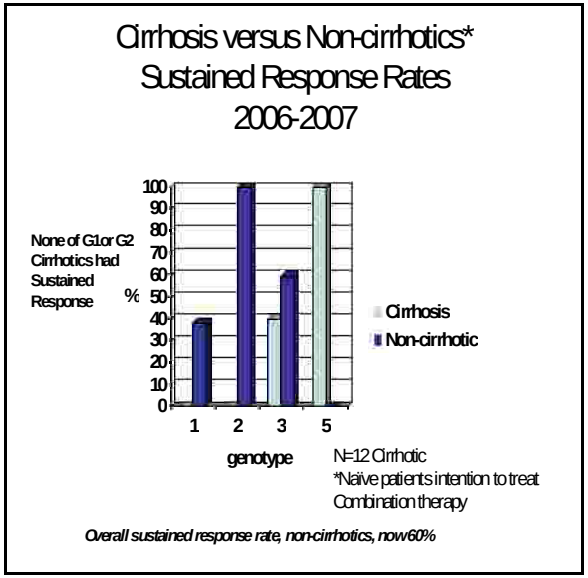
- **2001-2006**
- Total=212(190 naïve)
- Overall response
  - SR=53% R=24% NR=15%
- Cirrhotics
  - n=51(45 naïve)
  - Overall SR=33%
- Monotherapy,
  - n=5, (2pts SR)
- Retreated
  - n=17 (SR 35%)
- Coinfected
  - n=8 (5pts SR)

- **2006-2007**
- Total=60(54 naïve)
- Overall response
  - SR=50% R=23%NR=12%
- Cirrhotics
  - n=15 (12 naïve)
  - Overall SR=27%
- Monotherapy
  - n=2, (1 SR)
- Retreated
  - N=6 (SR 33%)
- Coinfected
  - n=2 (1pt SR)

Cirrhosis versus Non-cirrhotics* Sustained Response Rates



N=45 Cirrhotic
(4 did not complete)



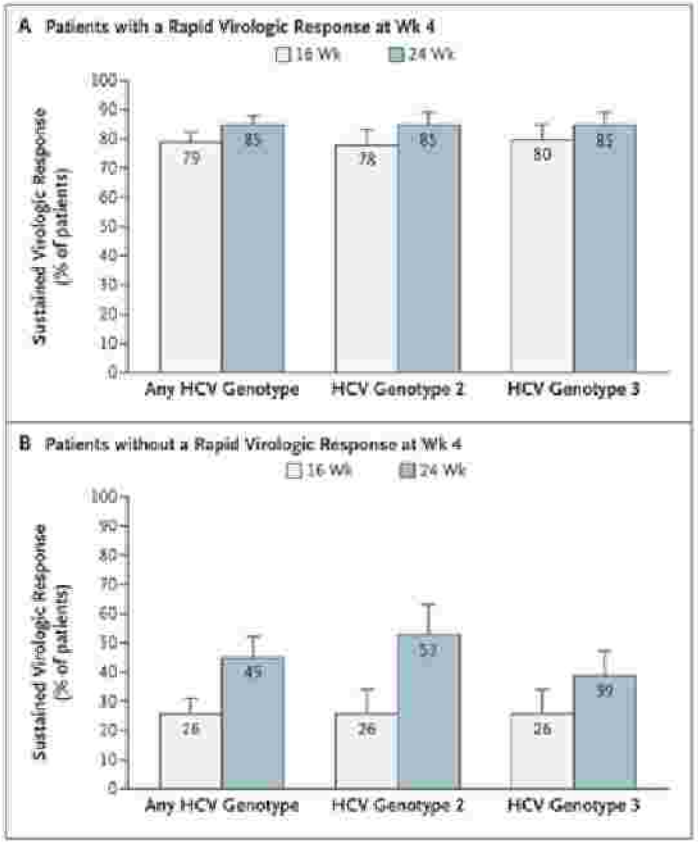
Reasons patients stopped treatment

18% n=11/60

	0-12 weeks	12-24 weeks	24-36 weeks	36-48 weeks	End of Rx-6month FU
Neutropaenia, thrombocytopaenia, anaemia	1				
Psychological		2		1	
Other reasons*	1	3			
Intolerable side effects	2		1		
Lost to follow up					3

Genotype 2 and 3

Can we shorten treatment…no?



Viral load < 400,000 IU/l SVR 81% for 16&24weeks

Shiffman NEJM 2007;357:124
Von Wagner M. Gastro 2005:129:522

Genotype 1
Outcome and viral kinetics

Viral Response	% with low VL	SVR with 48 weeks	
Negative at week 4	47%**	87%	Shorten therapy
Negative at week 12	**26%**	**38%**	**48 weeks**
Negative at week 24 (> 2 log drop week 12)	10%	10-20%	Lengthen
Positive at week 24	17%	0%	Stop

** 15% all genotypes

Ferenci P J Hep 2005; 43: 425

Genotype 1
Shortening treatment
Early viral response
10-15 % of all patients

Peg alpha 2a and Ribavirin 1000/1200mg

If RVR **PCR neg at week 4**

SVR at 24 weeks **86% genotype 4**
78% genotype 1

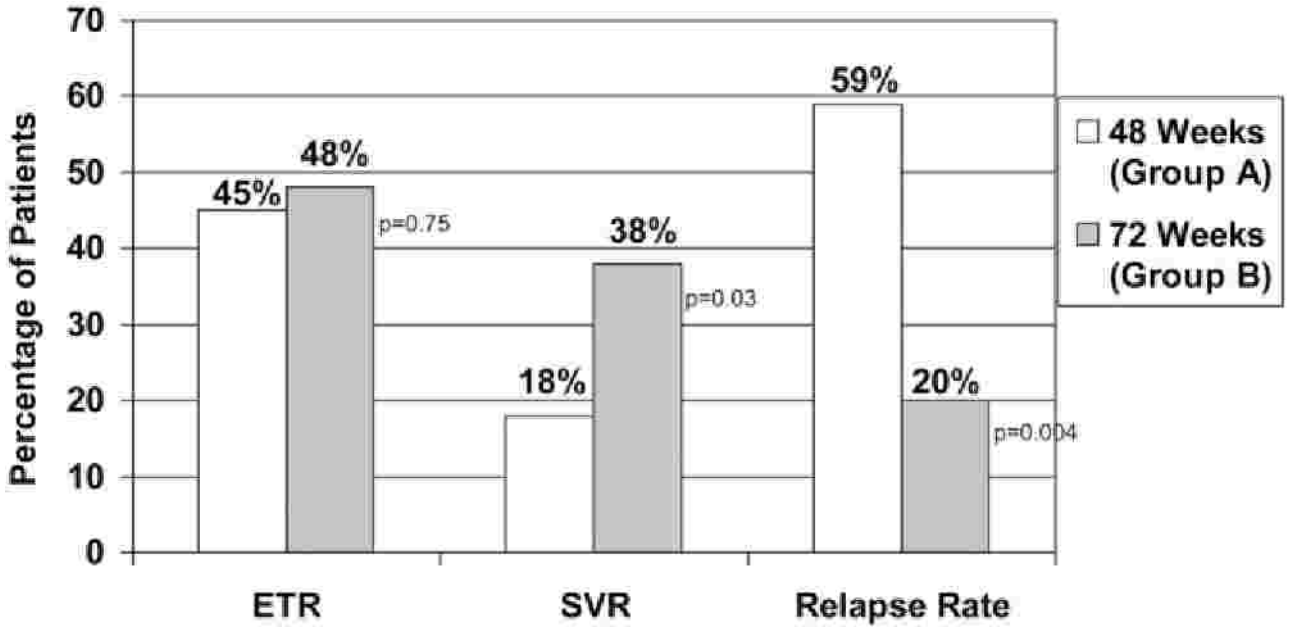
If RVR no predictors of SVR

Ferenci Gastro 2008; 135:431

Jensen. Hep 2006; 43:954
Zeuzem. J Hep2006; 44:97

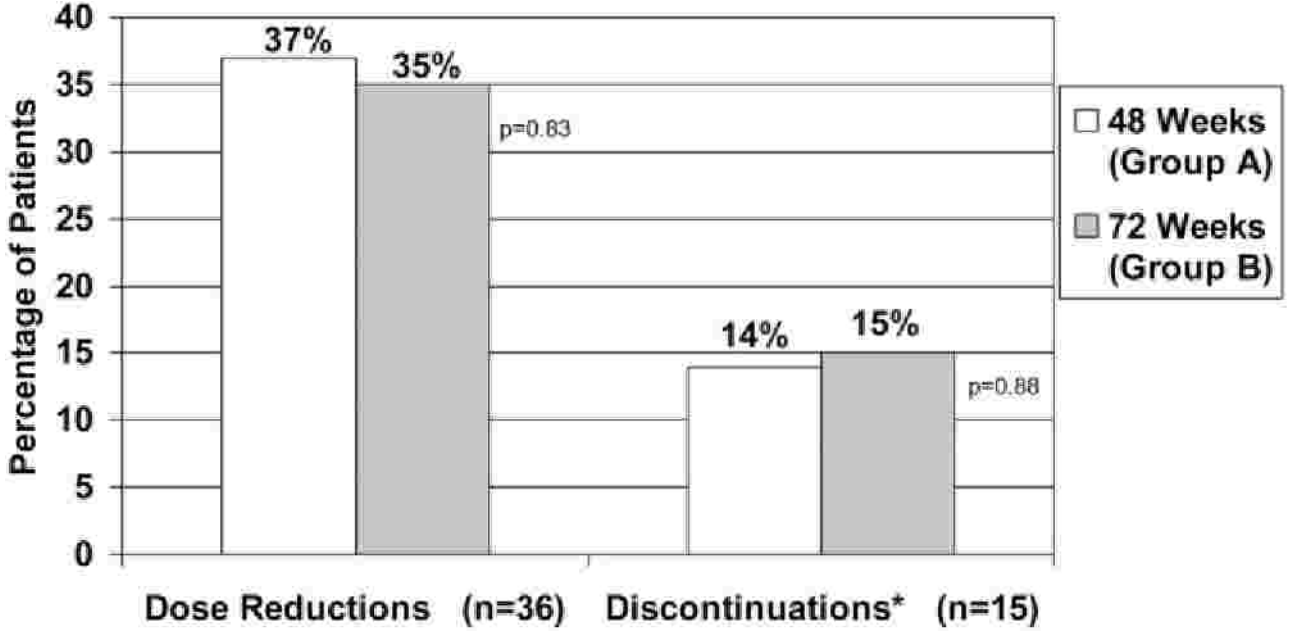
Genotype 1
Lengthening Treatment

Slow responders
2 log drop at week 12 and negative and negative week 24



Pearlman . Hpeatology 2007; 46: 1671
Berg T. Gastroenterology 2006; 130: 1086

Longer Treatment
Is it tolerable?



Tailored therapy
Genotype 1
Tinkering around the edges?

Peg 2a (weight dosing n=696); 237 standard 48w and 459 variable length as below

PCR neg at week 4 (26%)	24 weeks	77% SVR	v 87% 48w
PCR neg at week 8 (27%)	48 weeks	71% SVR	v 70% 48w
PCR neg at week 12 (11%)	72 weeks	63% SVR	v 38% 48w
Overall		49% SVR	v 45% 48w

If RVR at week 4 and viral load < 400,000

48 weeks 86% SVR
24 weeks 73% SVR

Mangia A Hep 2008; 47: 43-5-0

?? Reducing exposure to side-effects

Cirrhotics
Difficult to treat

104 Child-Pugh A cirrhosis from Sweden

SVR	genotype 1	13%
	Genotype 2	82%
	genotype 3	*38%*

46% had to stop early

Clinical Trial in process
24w v 48w

Syed E. Scand J Gastro 2008; 1-9

Treating Cirrhotics
Thrombopoeitin receptor antagonist

Table 2. Median Platelet Counts at the End of the Initial Treatment Phase and the End of the Antiviral Treatment Phase.*

Variable	Eltrombopag			Placebo (N=18)
	30 mg (N=14)	50 mg (N=19)	75 mg (N=23)	
End of initial treatment phase				
Platelet count				
No. of patients with data	11	16	22	14
Median — per mm³	125,000	212,000	204,000	53,000
Range — per mm³	40,000 to 214,000	47,000 to 599,000	78,000 to 527,000	34,000 to 74,000
Change from baseline				
No. of patients with data	12	16	22	14
Median — per mm³	74,000	152,000	151,000	−3,000
Range — per mm³	6,000 to 155,000	10,000 to 540,000	45,000 to 473,000	−22,000 to 13,000
≥100,000/mm³ — no. of responders/total no. of patients who could be evaluated (%)	9/12 (75)	15/19 (79)	20/21 (95)	0/17
≥200,000/mm³ — no. of responders/total no. of patients who could be evaluated (%)	3/12 (25)	9/19 (47)	11/21 (52)	0/17
End of antiviral treatment phase				
Platelet count				
No. of patients with data	2	7	8	1
Median — per mm³	106,000	100,000	92,000	39,000
Range — per mm³	43,000 to 164,000	46,000 to 156,000	38,000 to 245,000	39,000 to 39,000
Change from baseline — per mm³				
Median	31,000	54,000	31,000	−25,000
Range	−18,000 to 122,000	8000 to 97,000	−23,000 to 191,000	−25,000 to −25,000

* Data were not available for some patients because of withdrawal from the study before week 4 or for other reasons. Patients who could be evaluated were those whose data were included in the last-observation-carried-forward analysis in the intention-to-treat population and excluded those with a platelet count of less than 20,000 per cubic millimeter or 70,000 or more per cubic milliliter at baseline or those for whom the platelet count was unknown during the antiviral treatment phase. The overall P value for the treatment effect at the end of the initial treatment phase was less than 0.001, as were the P values for the comparison of each eltrombopag group with the placebo group with respect to the percentages of patients with platelet counts of 100,000 or more per cubic millimeter at the end of the initial treatment phase.

McHutchison.NEJM 2007;35:2227

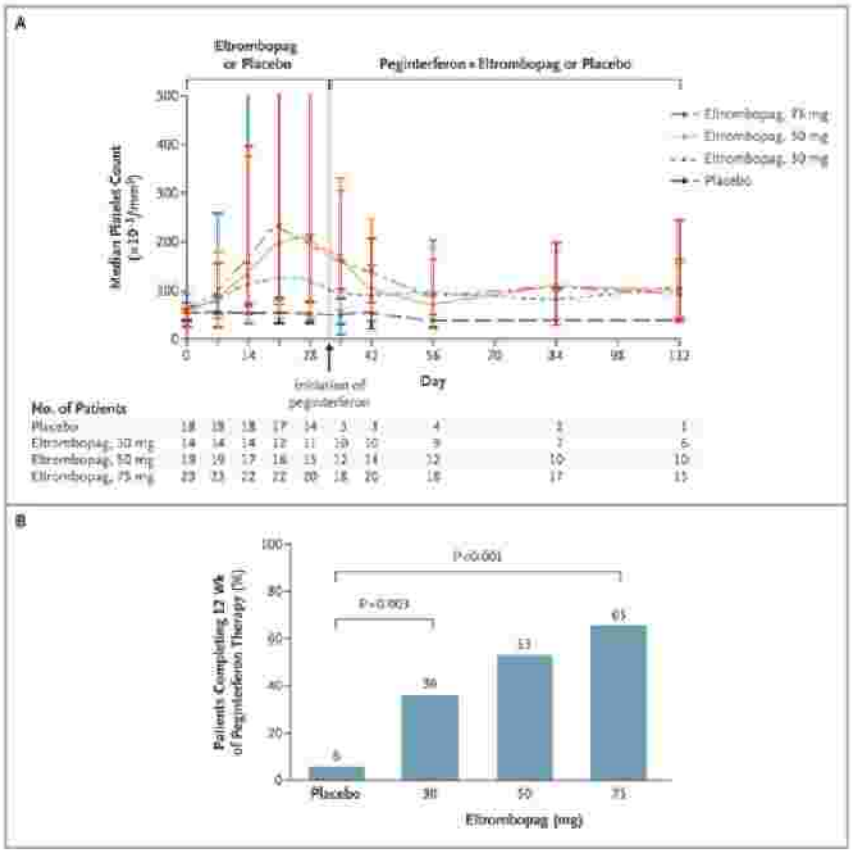
Do dose reductions contribute to poor response?

No controlled data on effect of growth factors widely used in Europe.

Concern about thromocytopaenia in our experience

Platelets 30-70 x10⁹/l
If > 100 after 1 month given interferon

Treating Cirrhotics



Effective

Lowest platelet count during therapy was 30

Durability of response

No data on whether leads to improved SR rate

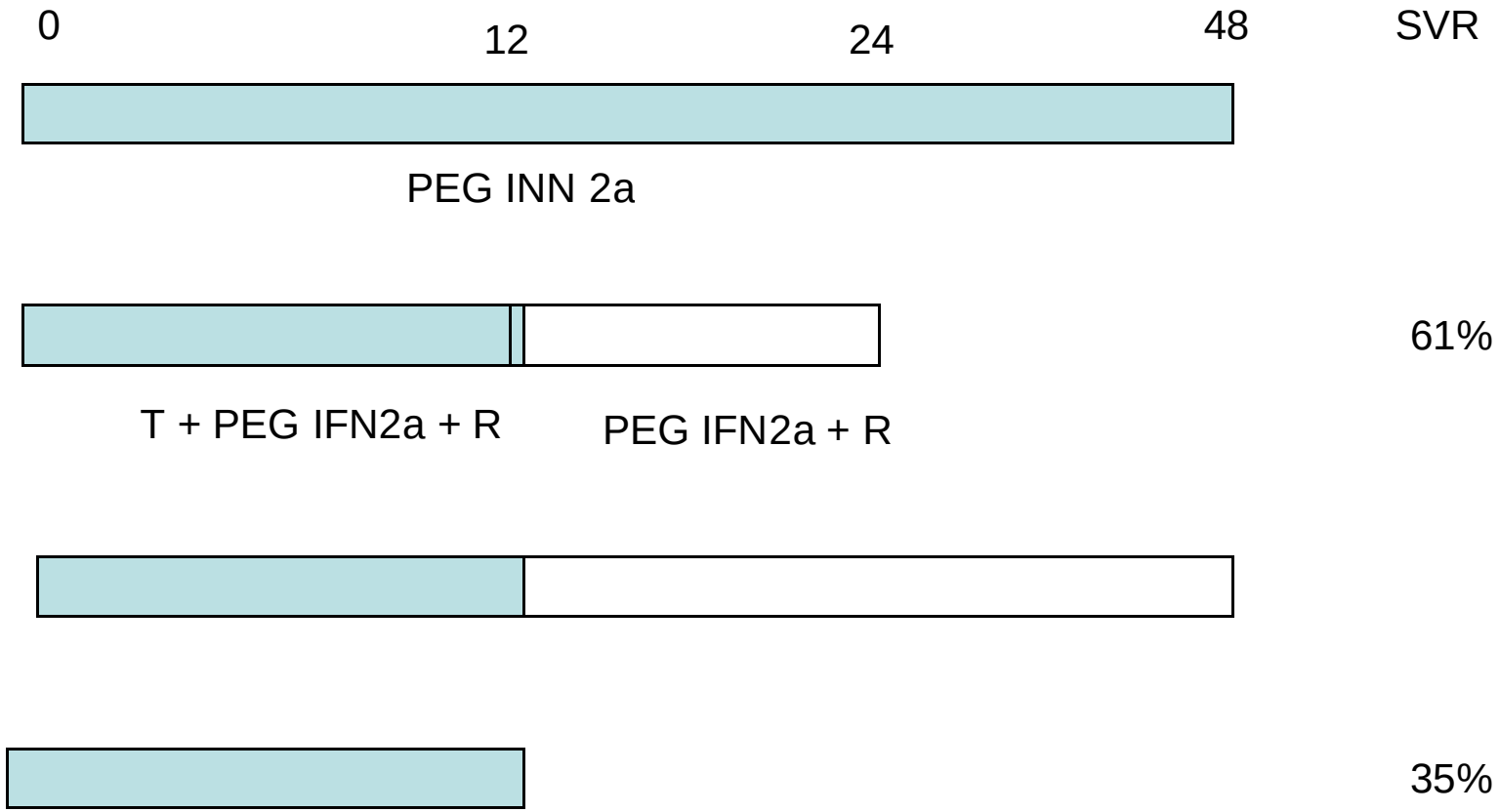
Side-effect of headache with High dose

Protease inhibitors
NS3/4a Inhibitors

- Ciluprevir
  - Cardiotoxicity/withdrawn
- Boceprevir
  - SPRINT 1
    - Need high dose ribavirin /can have a PEG/Rib lead in
- Telaprevir
  - Phase 2 studies (genotype 1, naïve)
    - PROVE 1 (US)
    - PROVE 2 (Europe)…..
      - ribavirin and telapravir only arm
      - Need ribavirin
      - 75% HCV RNA negative at 4 weeks

Dusheiko. J Hep 2008; 44: S26; McHutchison. J Hepatol 2008; 48:S4; Kwo. J Hepatol 2008; 44: S372

PROVE-1



HCV RNA neg week 12 (9%v 57%)

Genotype 1
Telaprevir tds

Protease inhibitors
Unanswered Questions

- Will every genotype1 patient need a protease inhibitor?
- Is additional Ribavirin and Peg-IFN needed with PI?
  - Ribavirin yes
- Role of lead in phase with Rib/IFN?
  - Those not needing triple therapy
- Length of protease inhibitor + overall treatment?
  - Probably 8-12 weeks of PI
  - Longer IFN if no EVR to treat mutant virius
- Resistance issues:
  - in those not obtaining a SVR?
  - compliance?
- Side effects?
  - Discontinuation with protease inhibitor 13% v 3%
  - Skin rashes in 15% some severe